CASE REPORT

Seizure as the Manifestation of Relapse of Multiple Sclerosis in a Military Pilot

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A case of a seizure in an active pilot with multiple sclerosis is presented. A 40-yr-old Canadian Forces pilot experienced a secondary generalized tonic-clonic seizure while taxiing a CC-130 (Hercules) transport after landing. His multiple sclerosis had been in remission since 1997 and he had been returned to restricted flying duties. He was assessed and treated, with no further seizures or adverse sequelae. An MRI showed a new demyelinating lesion in the anterior corpus callosum. His seizure was the only clinical manifestation of his MS relapse. The prevalence of seizures in MS patients, possible causal mechanisms, and the disposition of pilots with MS are discussed.

MULTIPLE SCLEROSIS (MS) and seizure disorders are relatively common diseases in the general population. There has been much debate in the medical literature as to whether there is a direct relationship between MS and seizures, and particularly the role, if any, of cortical and sub-cortical plaques in seizure pathogenesis. In the Canadian Forces, the mild relapsing-remitting type of MS does not preclude a pilot from active service, although limitations are applied to both deployability and operational flying. In the military and medical literature to date, there have been no reports of seizures in an active duty pilot with MS.

CASE REPORT

A 40-yr-old male, Canadian Forces pilot with a diagnosis of MS developed a generalized seizure while taxiing a CC-130 (Hercules) transport. After landing the aircraft, the pilot experienced a sudden onset of numbness and paresthesia of his left hand. This was followed by focal tonic-clonic activity of his left upper limb that progressed to a generalized tonic-clonic seizure lasting sixty seconds. Subsequently, he experienced a prolonged post-ictal period of 20 min duration and remained disoriented for 3 h. There was no incontinence or tongue biting. During the episode, his co-pilot took control of the aircraft. There were no injuries and the aircraft was undamaged.

En route to the Emergency Department, the pilot was disoriented and hypoxic (O_2 saturation = 80%), but stabilized on oxygen by mask with no further seizure episodes. He was afebrile and had no meningismus. On physical examination, there were no localizing signs or neurological deficits. A toxicology screen was negative. An ECG showed no acute changes. Chest X-ray, V/Q scan, and CT scan of the head were all normal. An EEG showed a non-specific, slow (delta waves) right temporal dysrhythmia. A diagnosis of first episode partial complex seizure with secondary generalization was made.

He was discharged home the next day with an MRI of the brain scheduled for that week. Compared with his last MRI in 2001, this study showed a new lesion in the anterior body of the corpus callosum consistent with demyelination, as well as persistent multiple punctate foci in the white mater bilaterally. Long-term seizure prophylaxis was not initiated.

Three days prior to this episode, he had complained of flu-like symptoms including malaise, myalgias, and a constant right-sided headache of moderate intensity. He was afebrile. He was on no regular medications and had no known drug allergies.

His past medical history is significant for multiple sclerosis, which had been in remission since diagnosis 5 yr previously. At that time, he presented with fatigue and progressive lower limb and saddle hypesthesia. These symptoms gradually resolved spontaneously over 3 wk. Interestingly, his brother had been diagnosed with MS 1 mo prior to the onset of these symptoms. A review of his history at that time revealed a 1-mo episode of mild diplopia in 1987 prior to CF enrollment. This symptom had been investigated including a lumbar puncture, visual evoked potentials, and EEG and a CT scan which were normal. The patient had no past history of seizures, nor any head injuries. There was no family history of seizure disorders.

A T2-weighted MRI of the spine showed hyperin-

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tense lesions at three levels (C1–2, C5–6 and T7–8). The patient was referred to a neurologist who made the diagnosis of MS based on these findings and an MRI of the brain that showed multiple lesions consistent with a demyelinating process. Visual-evoked potentials were normal.

He was grounded at that time. His symptoms resolved completely. After further investigations including a complete ophthalmologic assessment and neurocognitive testing, he was returned to restricted flying duties to fly with or as copilot in non-tactical strategic airlift duties only within Canada and continental U.S., no overseas or Arctic missions. Geographic deployability was restricted to fixed bases within Canada with physicians' services available. He continued flying with these restrictions and with 6-monthly clinical neurological follow-up, neurocognitive testing, and ophthalmological assessments until the current episode.

DISCUSSION

Multiple sclerosis and epilepsy are two of the most common neurological disorders. There has been debate in the medical literature whether seizures are more common in patients with MS. It is now generally accepted that the relative risk of seizures is significantly higher in MS than in the general population, although the absolute risk is small.

The prevalence of epilepsy in the general population is estimated to be 0.4–0.8% (4). There have been numerous case series and cohort studies examining the prevalence of seizures in MS patients. In a large series of 2,353 MS patients, Ghezzi et al. found that 2.33% of definite MS cases had a history of seizures (3). Nyquist et al. gave a seizure rate of 0.89% in their review of 5,715 MS cases from 1990 to 1998 (10), compared with a rate of 7.5% reported by Sokiæ et al. (13). Kinnunen and Wikström reported a figure of 3.5% in their prevalence cohort study of MS patients (5). These types of studies are often flawed with selection bias and many do not distinguish between the onset of epilepsy before a diagnosis of MS and those who developed epilepsy after MS diagnosis.

Three recent studies were conducted on the age-adjusted incidence of seizures in MS patients. Over a 25-yr period in Iceland, Olafsson et al. reported a threefold increase in the risk of developing epilepsy when compared with that expected in the general population (11). They also calculated the cumulative risk for developing epilepsy to be 0.5% by 5 yr and 1.9% by 10 and 15 yr. In contrast, a review of MS patients in Olmsted County, MN, showed no significant difference between the age-adjusted incidences of seizures in the two groups (9). Similarly, a Canadian study at five centers concluded that the cumulative incidence of seizures in MS is not significantly greater than the general population (7).

In a recent review of the literature, Poser and Brinar examined 29 studies of adult patients who had epileptic seizures and MS, representing a total of 17,239 clinical cases (12). Their analysis revealed a mean prevalence of 2.3%, about three to six times that in the general population. However, the authors noted that most studies did not define their diagnostic criteria for MS, nor did they clearly differentiate epileptiform activity from non-epileptic paroxysmal manifestations of MS.

A number of investigators have classified the types of seizures seen in MS patients. The most common presentation reported is a focal seizure with secondary generalization (14). Our case falls into this type, with a focal sensorimotor upper limb seizure generalizing to a full tonic-clonic seizure. However, most types of seizures have been described in MS patients, from aphasias to generalized status epilepticus (14). Some authors have also observed seizures to be the sole clinical manifestation of an MS relapse (13,15,16). Again, our pilot seems to exemplify this, as there were no other pre-event neurological symptoms or paroxysmal manifestations of MS.

The utility of electroencephalography (EEG) is variable in the literature. Ko et al. found EEG results to be very useful in evaluating MS patients with seizures (6). However, most EEGs in MS patients with seizures reveal either a normal pattern or generalized slowing (3,13). Focal changes (theta, delta waves, or spikes) are seen in the minority of such patients and often do not correspond to clinically localizing signs. Therefore, although the focal slowing in the right temporal lobe seen in our case corresponds to the left-sided onset of his seizure, this is against the norm for most patients.

Although the relative risk of seizures in MS patients in most studies is higher, the reasons for this are not entirely clear. Given that seizure disorders and MS are common diseases, the coincidental occurrence of idiopathic epilepsy and MS could account for some of the cases. It is possible that the single seizure episode observed in our pilot was unrelated to his MS. Alternatively, a number of authors have suggested that cortical and sub-cortical MS lesions may directly precipitate seizures (1,5,11,15). Our pilot did have a new plaque in the anterior corpus callosum, however, it is difficult to relate the anatomical location of this plaque to his seizure presentation. Furthermore, as his last MRI was in 2001, it is not known when this new plaque developed. Thompson et al. correlated MRI findings with onset of seizure activity (16). They described new or enhancing lesions involving the cortex and sub-cortical areas in six of seven patients studied. These lesions grew over a 4- to 6-wk period, then regressed slowly. The investigators concluded that the development of edema in critically located lesions may play a role in seizure production. In a similar study, Moreau et al. implicated sub-cortical MS plaques in the pathogenesis of seizure activity (8). Poser and Brinar were not convinced by the above evidence, pointing out that seizures are rare events in MS, despite the abundance of cortical and sub-cortical lesions seen in most MS patients (12).

Another explanation for the increased prevalence of seizures in MS is that latent epilepsy could be triggered by a relapse of MS. MS lesions induce a transient metabolic disturbance in the brain that may non-specifically trigger seizure activity in susceptible individuals (17). This theory is supported by cases of seizures temporally related to a relapse of MS, in that the metabolic effect of new MS lesions may induce epileptiform activity.

In general, the prognosis of seizures in MS is consid-

ered to be good, however, there have been no prospective studies looking at this. Kinnunen and Wikström reported that 48% of their MS patients had no further seizures after the first event, and in only three patients did the frequency of seizures increase over time (5). Whether or not to start seizure prophylaxis after the first seizure is also a matter of debate. Engelsen and Grønning found the occurrence of convulsive status epilepticus to be higher than expected in their MS population and thus recommend initiation of treatment after the first seizure (2). Spatt et al., however, propose anti-convulsant therapy only after two or three seizures separated by at least 1 d (14). They do not recommend prophylactic treatment of seizures that appear as a symptom of an MS relapse. Based on their review of the literature, event-related seizures have only a weak predictive value for the development of chronic epilepsy. Similarly, Poser and Brinar concluded that anti-convulsant therapy should be started only if seizures recur after an acute bout of MS (12).

In summary, it is established that the prevalence of seizures in MS is significantly higher than in the general population, thus MS must play a role in provoking seizure activity in these individuals. It remains unclear whether MS plaques (or the associated local metabolic changes) directly cause seizures or whether MS non-specifically triggers latent epilepsy.

In most military aeromedical jurisdictions, the diagnosis of multiple sclerosis results in permanent grounding. Civilian agencies including Transport Canada and the FAA may issue special issuance medical certificates for relapsing remitting MS provided the episodes are infrequent and there are no functional nor neuropsychological deficits. United States Air Force, U.S. Navy, and U.S. Army regulations require aviators to be permanently grounded with the diagnosis of multiple sclerosis. Aviators with a single episode of optic neuritis may be returned to flying duties. In the Canadian Forces, pilots with relapsing, remitting MS have been considered on a case-by-case basis. Pilots with very infrequent relapses, have on occasion, as in this case, been retained on restricted flying duties. Criteria for continuing restricted flying duties have included normal biannual assessments including clinical examination, detailed ophthalmologic assessment, and neurocognitive testing, with MRI studies biennially.

SUMMARY

A case of a seizure 5 yr after diagnosis of MS in a male Canadian Forces pilot has been presented. His partial complex seizure with secondary generalization follows the typical pattern for such patients. This seizure was the only manifestation of an MS relapse, other than the appearance of a new cortical lesion on MRI and non-specific antecedent symptoms. His EEG points to the right temporal lobe as the origin of seizure activity, so it is difficult to directly implicate a plaque in the anterior portion of the corpus callosum in causing a seizure. It is more likely that this plaque triggered a seizure through a non-specific mechanism by altering the cerebral metabolic environment.

Our pilot has not had any further seizure episodes to date, suggesting a favorable prognosis. However, prospective studies of the prognosis of seizures in MS patients are needed to clarify this issue. Meanwhile, he has been permanently grounded. This case supports a conservative approach to a return to even restricted flying in pilots with MS, regardless of the duration of their remission. In the Canadian Forces, this case will undoubtedly result in a more circumspect approach in any future cases.

REFERENCES

1. Bolay H, Ay H, Saygi S, et al. Late-onset absence seizures in multiple sclerosis: a case report. Clin Electroencephalogr 1995; 26:124–30.
2. Engelsen BA, Grønning M. Epileptic seizures in patients with multiple sclerosis. Is the prognosis of epilepsy underestimated? Seizure 1997; 6:377–82.
3. Ghezzi A, Montanini R, Basso PF, et al. Epilepsy in multiple sclerosis. Eur Neurol 1990; 30:218–23.
4. Hauser W. Epidemiology of epilepsy. In: Gorelick P, Alter M, eds. Handbook of neuroepidemiology. New York: Marcel Dekker; 1994:325.
5. Kinnunen E, Wikström J. Prevalence and prognosis of epilepsy in patients with multiple sclerosis. Epilepsia 1986; 27:729–33.
6. Ko DY, Lublin F. Seizures and epilepsy in multiple sclerosis. Epilepsia 1996; 37(Suppl. 5):15.
7. Mandalfino P, Koopman WJ, Vandervoort MK, et al. Seizures in multiple sclerosis: a multi-centre study. Mult Scler 1998; 4:520.
8. Moreau T, Sochurkova D, Lemesle M, et al. Epilepsy in multiple sclerosis: radiological-clinical correlations. Epilepsia 1998; 39: 893–6.
9. Nyquist PA, Cascino GD, McClelland RL, et al. Incidence of seizures in patients with multiple sclerosis: a population-based study. Mayo Clin Proc 2002; 77:910–2.
10. Nyquist PA, Cascico GD, Rodriguez M. Seizures in patients with multiple sclerosis seen at Mayo Clinic, Rochester Minn, 1990–1998. Mayo Clin Proc 2001; 76:983–6.
11. Olafsson E, Benedikz J, Hauser WA. Risk of epilepsy in patients with multiple sclerosis: a population-based study in Iceland. Epilepsia 1999; 40:745–7.
12. Poser CM, Brinar VV. Epilepsy and multiple sclerosis. Epilepsy Behav 2003; 4:6–12.
13. Sokiæ DV, Stojsavljeviæ N, Druloviæ J, et al. Seizures in multiple sclerosis. Epilepsia 2001; 42:72–9.
14. Spatt J, Chaix R, Mamoli B. Epileptic and non-epileptic seizures in multiple sclerosis. J Neurol 2001; 248:2–9.
15. Spatt J, Coldenberg G, Mamoli B. Simple dysphasic seizures as the sole manifestation of relapse in multiple sclerosis. Epilepsia 1994; 35:1342–5.
16. Thompson AJ, Kermode SG, Moseley IF, et al. Seizures due to multiple sclerosis: seven patients with MRI correlations. J Neurol Neurosurg Psychiatry 1993; 56:1317–20.
17. Waxman S. Multiple sclerosis as a neuronal disease. Arch Neurol 2000; 37:22–3.